World J Urol (2003) 21: 21–27
DOI 10.1007/s00345-002-0314-z

TOPIC PAPER

Eric A. Klein · Scott M. Lippman · Ian M. Thompson
Phyllis J. Goodman · Demetrius Albanes
Philip R. Taylor · Charles Coltman

The Selenium and Vitamin E Cancer Prevention Trial

Received: 26 November 2002 / Accepted: 29 November 2002 / Published online: 8 March 2003

Abstract *Background:* Evidence suggests that both selenium and vitamin E reduce the risk of prostate cancer. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a randomized, prospective, double-blind study designed to determine whether selenium and vitamin E alone and in combination can reduce the risk of prostate cancer among healthy men. *Materials and methods:* The preclinical and epidemiological evidence supporting a role for selenium and vitamin E as chemopreventive agents in prostate cancer are reviewed, and details of the trial design are presented. *Results:* Preclinical, epidemiological, and phase III data from randomized, placebo-controlled clinical trials suggest that both selenium and vitamin E have potential efficacy in prostate cancer prevention. SELECT is a 2×2 factorial study with an accrual goal of 32,400 men with nonsuspicious DRE and serum PSA of 4 ng/ml or lower. *Conclusions:* SELECT is the second large-scale study of chemoprevention for prostate cancer. Enrollment began in 2001 with final results anticipated in 2013.

Keywords Prostate cancer · Chemoprevention · Selenium · Vitamin E

E. A. Klein (✉)
Section of Urologic Oncology, Urological Institute,
Cleveland Clinic Foundation, 9500 Euclid Avenue,
Cleveland, OH 44195, USA
E-mail: kleine@ccf.org

S. M. Lippman
Department of Clinical Cancer Prevention,
M.D. Anderson Cancer Center,
Houston, TX, USA

I. M. Thompson
Division of Urology,
University of Texas Health Sciences Center,
San Antonio, TX, USA

P. J. Goodman
Southwest Oncology Group Statistical Center,
Fred Hutchinson Cancer Research Center,
Seattle, WA, USA

D. Albanes · P. R. Taylor
Cancer Prevention Studies Branch,
Division of Clinical Sciences,
National Cancer Institute, Washington, DC, USA

C. Coltman
Southwest Oncology Group,
San Antonio, TX, USA

Prostate cancer has been the most common visceral malignancy in men in the United States for the past decade. The estimated life-time risk of disease is 16.6% in whites and 18.1% in African-Americans, with a life-time risk of death of 3.5% and 4.3%, respectively [43]. The dramatic increase in the incidence of prostate cancer associated with prostate-specific antigen (PSA) based screening regimens, relatively stable mortality rates, and treatment-associated morbidity have piqued interest in developing ways of preventing this disease. Recognition that androgens are important in the development of prostate cancer led to the first large-scale population-based prevention study, the Prostate Cancer Prevention Trial (PCPT, SWOG-9217). PCPT is an ongoing phase III, double-blind, placebo-controlled, randomized trial to determine the efficacy of finasteride in reducing the period prevalence of prostate cancer. PCPT opened in 1993 and easily exceeded the goal of 18,000 randomized men during a 3-year accrual period. Final results of this trial are expected in 2004.

Recent research suggests that selenium and vitamin E are promising candidates for prostate cancer prevention, based primarily on secondary analyses of large-scale chemoprevention trials for other cancers [9, 21]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is an intergroup phase III, randomized, double-blind, placebo-controlled, population-based clinical trial designed to test the efficacy of selenium and vitamin E alone and in combination in the prevention of prostate cancer.

Rationale for study agents

Selenium

Selenium is a nonmetallic trace element recognized as a nutrient essential to human health. Selenium is an essential constituent of at least four extracellular and cellular glutathione peroxidases, three thyroidal and extrathyroidal iodothyronine 5′deiodinases, thioredoxin reductase, and other selenoproteins. Typical dietary intake of selenium in the United States is 80–120 μg/day, and the recommended dietary allowance is 557 μg/day [37].

Selenium inhibits tumorigenesis in a variety of experimental models [12, 36]. Of the more than 100 reported studies in more than two dozen animal models two-thirds have shown reductions in tumor incidence in response to selenium supplementation. Selenium inhibits the growth of DU-145 human prostate carcinoma cells in vitro, selenoproteins are downregulated in some transgenic mouse models and human prostate cancers, and oral selenium is selectively taken up by the prostate in humans [7, 53]. There are a number of potential mechanisms proposed for the antitumorigenic effects of selenium, including antioxidant effects, enhancement of immune function, induction of apoptosis, inhibition of cell proliferation, alteration of carcinogen metabolism, cytotoxicity of metabolites formed under high-selenium conditions, and an influence on testosterone production [3, 16, 23, 26, 42, 45, 47]. The bioactive form of selenium active in chemopreventive models appears to be methylselenol, which can be derived from ingestion of either inorganic or organic forms [24].

Epidemiological evidence suggests that selenium status is inversely related to the risk of at least some cancers, including gastrointestinal malignancies and prostate cancer [12]. A recent nested case-control study found that the risk of advanced prostate cancer was reduced by one-half to two-thirds for men with the highest selenium status [31, 56].

Two large, randomized trials have reported findings relevant to selenium supplementation and cancer [4, 10]. In the Nutrition Intervention Trial conducted among more than 29,000 individuals aged 40–69 years from the general population in Linxian, China, selenium (50 μg/day) in combination with vitamin E (30 mg/day) and β-carotene (15 mg/day) led to a 13% reduction in mortality from cancers at all sites and a 21% reduction in mortality from stomach cancer. In the second trial, also conducted in Linxian, investigators tested the hypothesis that a multivitamin/mineral (including selenium, 50 μg/day) plus β-carotene (15 mg/day) would reduce the risk of esophageal/gastric cardia cancer in a population of more than 3,000 individuals with esophageal dysplasia [31]. In this population total cancer mortality was 7% lower and esophageal cancer was 14% lower in the supplemented group. The independent effect of selenium and the impact of supplementation on prostate cancers could not be evaluated in these trials because of the trial design and the small numbers of cases in the study population.

Recent enthusiasm for selenium in the prevention of prostate cancer comes from the clinical trial conducted by Clark [9]. In this study 1312 subjects with a prior history of skin cancer were randomized to receive 200 μg/day selenium in the form of selenized yeast or placebo and followed for an average of 4.5 years for the development of basal or squamous cell carcinoma of the skin and other cancers. While no difference was noted in rates of skin cancer, further analysis found that prostate cancer incidence was reduced by two-thirds among those in the selenium supplemented group. Based on a small number of cases additional stratified analyses suggested a greater reduction in prostate cancer in those having low baseline selenium blood levels, those less than 65 years old, and those with low serum PSA values [10]. There also were significant reductions in lung and colon cancer incidences in this trial [56].

Vitamin E (α-tocopherol)

Vitamin E is a family of naturally occurring, essential, fat-soluble vitamin compounds. Its importance in mammalian biology was first revealed by earlier fertility research [17]. Vitamin E functions as the major lipid-soluble antioxidant in cell membranes; it is a chain-breaking, free-radical scavenger and inhibits lipid peroxidation specifically, biological activity relevant to carcinogen-induced DNA damage [6]. The most active form of vitamin E is α-tocopherol; it is also among the most abundant and is widely distributed in nature and the predominant form in human tissues [33, 41].

α-Tocopherol may influence the development of cancer through several mechanisms. It has a strong inherent potential for antioxidation of highly reactive and genotoxic electrophyles, such as hydroxyl, superoxide, lipid peroxyl and hydroperoxyl, and nitrogen radicals, thereby preventing propagation of free radical damage in biological membranes and decreasing mutagenesis and carcinogenesis [6]. Vitamin E also blocks nitrosamine formation. α-Tocopherol inhibits protein kinase-C activity and the proliferation of smooth muscle cells and melanoma cells [2, 8, 34, 40]. Vitamin E also induces the detoxification enzyme NADPH:quinone reductase in cancer cell lines and inhibits arachadonic acid and prostaglandin metabolism [48, 52]. Effects on hormones which can increase cellular oxidative stress and proliferative activity and on cell-mediated immunity have also been reported [48].

Studies suggest that vitamin E can inhibit the growth of certain human cancer cell lines, including prostate, lung, melanoma, oral carcinoma, and breast, while animal experiments show prevention of various chemically induced tumors, including hormonally mediated tumors [25, 27, 46, 49]. The same studies showed vitamin E to slow the growth of prostate tumors in vitro and in vivo

in rats receiving various doses of chemotherapeutic agents [25, 27, 46, 49].

The average dietary vitamin E intake among men and women in the United States is estimated to be 10 mg/day and 7 mg/day, respectively [50, 51]. The recommended dietary allowance of the National Research Council are set at 10 mg for men and 8 mg for women daily [38].

Evidence currently suggests that vitamin E status or intake is inversely related to risk of lung and colorectal cancers. Of the six cohort studies of lung cancer four reported that the prediagnostic serum vitamin E level was lower in those who subsequently developed cancer than in noncases, and one reported no differences in baseline dietary intake between cases and noncases or a weakly protective association for supplemental vitamin E [13, 44, 55]. In two other cohorts vitamin E intake was not associated with lung cancer [29, 39]. Five prospective studies examined the association between serum α-tocopherol and colorectal cancer, and in general serum levels were lower in those who subsequently developed colorectal cancer than in noncases. A pooled estimate of 40% lower risk has been reported for the highest compared to the lowest category of serum α-tocopherol concentration [32]. By contrast, prospective studies show no association between dietary vitamin E intake and incidence of colon or colorectal cancer, although one of these among women in Iowa showed a 50% reduction in colon cancer incidence for vitamin E supplement use, and an estimated relative risk of 0.32 for the highest vs. lowest quintile of vitamin E intake from diet plus supplements [5, 54]. One case-control study conducted in Italy reported a significant inverse association for higher vitamin E intake or for at least 200 IU daily (vs. none), while the findings from several others reveal no substantive relationship with colorectal cancer [18, 19, 30, 35].

Observational studies are inconsistent with regard to a beneficial association between serum vitamin E and prostate cancer. These studies have assessed cancer risk through estimated dietary intake or through determination of plasma or serum α-tocopherol concentrations. Of the few prospective studies having a sufficient number of prostate cancers for analysis two reported no dose-response association, and one reported a statistically significant protective association [11, 14, 28]. A study of 2,974 subjects over a 17-year follow-up period found low α-tocopherol to be associated with higher prostate cancer risk [22]. These studies all noted lower serum or plasma vitamin E concentrations among prostate cancer cases years prior to diagnosis [11, 14, 28]. In a cohort analysis the associations between prostate cancer and baseline serum and dietary α-tocopherol differed significantly according to the α-tocopherol intervention status, with the suggestion of a protective effect for total vitamin E intake among those men who also received α-tocopherol supplementation [15]. One case-control study reported no association between vitamin E intake and risk of prostate cancer [20].

One large-scale randomized, placebo-controlled trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC), supports the role of vitamin E in the prevention of prostate cancer. ATBC was a randomized, double-blind, placebo-controlled trial of α-tocopherol (50 mg synthetic DL-α-tocopheryl acetate daily) and β-carotene (20 mg daily; alone or in combination) among 29,133 male smokers 50–69 years old at entry [15, 21]. During the median follow-up period of 6.1 years there were 246 new cases and 64 deaths from prostate cancer. Among those assigned to the α-tocopherol arm ($n = 14{,}564$) there were 99 incident prostate cancers, compared with 147 cases among those assigned to the non-α-tocopherol arm ($n = 14{,}569$)[1,21]. This represented a statistically significant 32% reduction in prostate cancer incidence (95% confidence interval, 12–47%; $P = 0.002$). The observed preventive effect appeared stronger in clinically evident cases, where the incidence was decreased 40% in subjects receiving α-tocopherol (95% confidence interval, −20% to −55%). Prostate cancer mortality data, although based on fewer events, suggested a similarly strong effect of 41% lower mortality (95% confidence interval, −1% to −64%). Although the incidence of prostate cancer was only a secondary endpoint in this trial, these findings suggest a potentially substantial benefit of α-tocopherol in reducing the risk prostate cancer.

SELECT

SELECT is a double-blind, placebo-controlled, 2×2 factorial study (Fig. 1) of selenium and vitamin E alone and in combination in 32,400 healthy men with a digital rectal examination (DRE) not suspicious for cancer and a serum PSA level of 4 ng/ml or less. Whites aged 55 years or over and African-Americans 50 years or over are eligible, reflecting a higher age-adjusted incidence of prostate cancer in the latter group. Further criteria include: no prior history of prostate cancer or high-grade PIN, no anticoagulation therapy except low-dose aspirin, normal blood pressure (systolic BP < 160 mmHg, diastolic BP < 90 mmHg), and

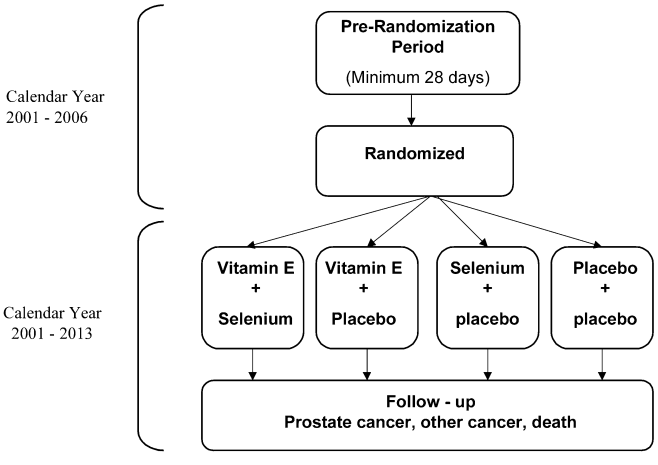

Fig. 1 Schema of study

willingness to restrict supplementation of selenium and vitamin E during participation. Randomization will be equally distributed among the four study arms, with intervention consisting of a daily oral dose of study supplement and/or matched placebo (Fig. 1). Study duration will be 12 years, with a 5-year uniform accrual period and a minimum of 7 and maximum of 12 years of intervention depending on the time of randomization.

The study supplements are 200 μg L-selenomethionine, 400 mg racemic α-tocopheryl, and an optional multivitamin containing no selenium or vitamin E. The racemic mix of α-tocopheryl will include both the D- and L-isomers.

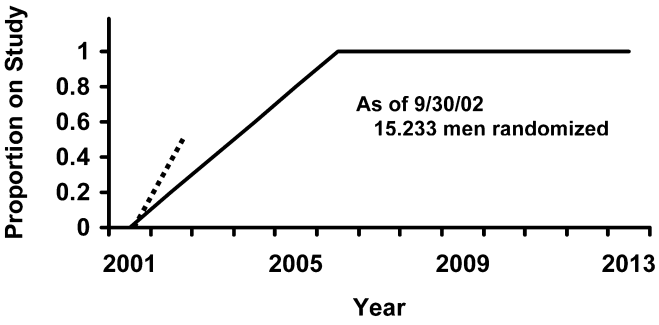

Fig. 2 Accrual to SELECT. *Solid line* Planned accrual; *dotted line* actual accrual thru 30 September 2002

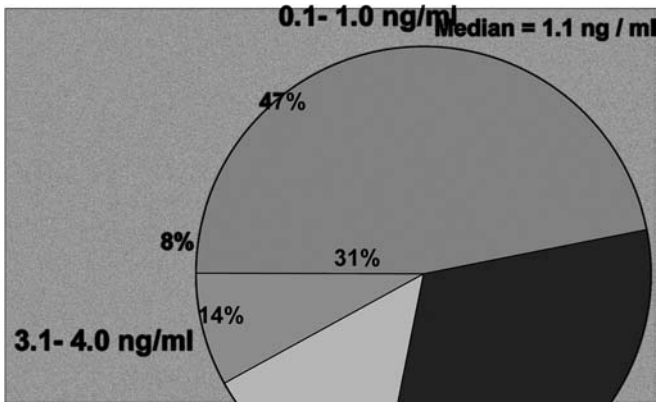

Fig. 3 PSA distribution at time of enrollment

Study endpoints

The primary endpoint for the trial is the clinical incidence of prostate cancer as determined by a recommended routine clinical diagnostic work-up, including yearly DRE and serum PSA level. A centrally reviewed histological diagnosis of prostate cancer will be required in all cases, except for those based on a total PSA higher than 50 ng/ml and a positive bone scan. Prostate biopsy will be performed at the discretion of study physicians according to local community standards. The study protocol recommends biopsy for study participants who have a DRE suspicious for cancer and/or for elevations in serum PSA. Unlike the PCPT, no biopsy will be required at the end of SELECT. Secondary endpoints will include prostate cancer-free survival, all-cause mortality, and the incidence and mortality of other cancers (e.g., lung, colorectal) and diseases (including serious cardiovascular events) potentially impacted by the chronic use of selenium and vitamin E. Other trial objectives will include periodic quality-of-life assessments, assessment of serum micronutrient levels and prostate cancer risk, and studies of the evaluation of biological and genetic markers with the risk of prostate cancer.

Accrual and participant characteristics

As of 31 January, 2003, a total of 18,881 men were enrolled and randomized on SELECT, representing $>50\%$ of the total planned accrual of 32,400 and substantially exceeding the projected accrual rate (Fig. 2). Of these enrollees more than 95% have completed high school and more than 80% at least some college. Twelve percent of the enrollees are African-American. PSA distribution of the enrollees is shown in Fig. 3.

Statistical considerations

Sample size calculation

The primary analysis of the study includes five prespecified comparisons: (a) vitamin E vs. placebo, (b) selenium vs. placebo, (c) combination (vitamin E plus selenium) vs. placebo, (d) combination vs. vitamin E, and (e) combination vs. selenium. The study design will permit detection of a 25% reduction in the incidence of prostate cancer for selenium or vitamin E alone, with an additional 25% reduction for the combination of selenium and vitamin E compared to either agent alone. The study allows for the potential interaction between vitamin E and selenium, and additional statistical analyses will include tests for vitamin E vs. no vitamin E, selenium vs. no selenium, and for interactions between the two agents. The overall α level for the study is 5% (two-sided), with each of the five comparisons tested at the 1% level to maintain an overall 5% level for the study. With a sample size of 32,400, the estimated power for the comparison of a single agent vs. placebo is 96% and the power for the comparison of an effective single agent vs. the combination of selenium and vitamin E is 89% (Table 1). The median time under observation is estimated to be 8.8 years.

Incidence rate

Based on PCPT, expectations are that participants will have a median age of 63 years at study entry. The yearly prostate cancer incidence figures used in the sample-size calculations are derived from observations of the PCPT

Table 1 Power calculations (*PCPT* Prostate Cancer Prevention Trial, *SEER* Surveillance, Epidemiology, and End Results)

Comparison	Baseline hazard (incidence)	Relative risk reduction (%)	Power (%)
Single agent vs. placebo	PCPT/SEER	25	96
Placebo vs. combination	PCPT/SEER	44	>99
Effective single agent vs. combination	0.75 x PCPT/SEER	25	89

Table 2 Expected incidence of prostate cancer in each arm under the alternative hypothesis

	Number at risk	Proportion with prostate cancer	Number with prostate cancer
Placebo	8100	0.066	533
Vitamin E	8100	0.050	403
Selenium	8100	0.050	403
Vitamin E + selenium	8100	0.038	304

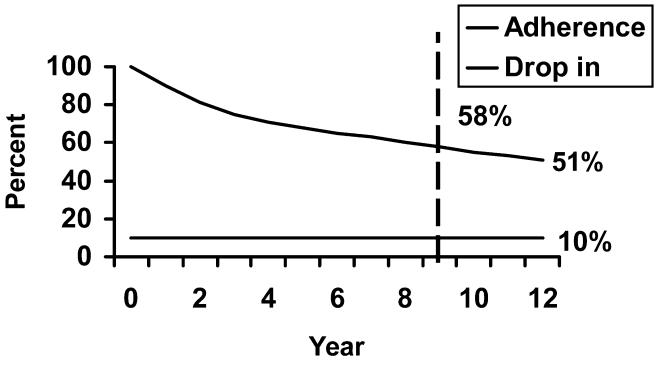

Fig. 4 Medication and drop-in rates

and SEER databases. The estimated incidence of prostate cancer begins at 0% at randomization, reaches 0.14% at year 1, and rises steadily to 1.36% 12 years later. The number of prostate cancer cases expected in each study arm is listed in Table 2, based on 8100 participants per arm.

Medication rate

Medication rate is an estimate of the percentage of participants who actually take the study supplements. It is quantified as the percentage of full active drug dose taken by men in each arm. It is assumed that the medication rate will vary over time, with a decline from 100% after randomization to 51% at the end of 12 years of treatment (Fig. 4). These estimates are based on observed rates in the PCPT. Compliance with daily medication use in SELECT may be higher than PCPT because finasteride has more side effects than is known for selenium or vitamin E.

Drop-in rate

The drop-in rate, defined as the rate of those randomized to placebo who obtain and take selenium and/or vitamin E on their own, is assumed to be constant at 10% for the 12 years of treatment (Fig. 4). Recent Heart Outcomes Prevention Evaluation (HOPE) data support this estimate [57]. A drop-in rate of 15% reduces the power to 92% for the comparison of placebo to either single agent and 82% for an effective single agent vs. the combination.

Competing risks-death and loss

The cumulative competing risk is defined to be the estimated cumulative all-cause mortality rate plus the cumulative lost-to-follow-up (LTFU) rate. The mortality

Table 3 Differences between the PCPT and SELECT study designs

Variable	PCPT	SELECT
Agent	Finasteride	L-Selenomethionine and α-tocopherol
Eligibility criteria		
Age (years)	≥55 years	≥50 years for African-Americans; > 55 all others
DRE	Not suspicious	Not suspicious
Total PSA (ng/ml)	≤3.0	≤4.0
Primary endpoint	7-year prevalence	Incidence
Placebo run-in	Yes	No
Follow-up intervals	Every 3 months	Every 3 months year 1, then every 6 months
Disease ascertainment	Biopsy recommended for PSA >4.0 and suspicious DRE during the trial EOS	Biopsy recommended per community standard
End-of-study biopsy	Yes	No
Central laboratory facility	All PSAs	None
Pathology review	All biopsies	Prostate cancers only (and negative prostate biopsies in a subset only)
Quality-of-life studies	All participants	Subset only
Secondary endpoints	Prostate cancer and screening issues	All cancer issues
African-American participation	4%	Planned 20%

rates used were taken from PCPT for the first 4 years of treatment and then adjusted upwards to the 1995 rates for all races in the United States. The LTFU rate was calculated to be 0.5% per year. The cumulative loss (death plus LTFU) is expected to be 0.8% at the end of the first year of the study and 33.2% by the end of year 12.

Other factors

In contrast to finasteride, it is assumed that the supplements being tested in SELECT do not affect PSA or prostate size, either of which could bias the diagnosis of prostate cancer. PSA levels at baseline and after 2 years of vitamin E use were analyzed on a subsample of participants from the HOPE trial and after 3 years in the ATBC study (unpublished observations). There was no evidence of an effect on the PSA concentrations in these studies.

Differences between SELECT and PCPT

The experience with PCPT has influenced the design of SELECT. These differences include broader eligibility criteria, elimination of the placebo run-in period, less frequent follow-up contacts, and reliance on community standards for the diagnosis of prostate cancer (Table 3). These changes reflect the larger sample size for SELECT, the minimal side effects expected with the study agents, and an effort to simplify data management. Because PCPT requires yearly DRE, PSA, and an end-of-study biopsy, its secondary endpoints will yield information on PSA-induced lead-time bias, PSA velocity, and other measures of PSA-based screening as well as information on the natural history of benign prostatic hyperplasia. In contrast, the secondary endpoints of SELECT focus on incidence and mortality of cancers potentially impacted by the use of selenium and vitamin E.

Summary

Ample evidence exists from preclinical studies, epidemiological observations, and controlled and uncontrolled clinical trials that selenium and vitamin E may prevent the development or progression of prostate cancer. SELECT is a large-scale, population-based, randomized controlled trial which will directly test the effect of these agents alone and in combination on the incidence of prostate cancer in North American men.

References

1. ATBC Cancer Prevention Study Group (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 330:1029–1035
2. Azzi A, Boscoboinik D, Marilley D, Ozer NK, Stauble B, Tasinato A (1995) Vitamin E: a sensor and an information transducer of the cell oxidation state. Am J Clin Nutr 62:1337S–1346S
3. Bedwal RS, Nair N, Sharma MP, Mathur RS (1993) Selenium – its biological perspectives. Med Hypotheses 41:150–159
4. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY, Yu Y, Liu BQ, Tangrea J, Sun YH, Liu F, Fraumeni JF Jr, Zhang YH, Li B (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85:1483–1492
5. Bostick RM, Potter JD, McKenzie DR, et al (1993) Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study. Cancer Res 53:4230–4237
6. Burton GW, Ingold KU (1981) Autoxidation of biological molecules. I. The antioxidant activity of vitamin E and related chain-breaking phenolic antioxidants in vitro. J Am Chem Soc 103:6472
7. Calvo A, Xiao N, Kang J, Best CJ, Leiva I, Emmert-Buck MR, Jorcyk C, Green JE (2002) Alterations in gene expression profiles during prostate cancer progression: functional correlations to tumorigenicity and down-regulation of selenoprotein-P in mouse and human tumors. Cancer Res 62:5325–5335
8. Chatelain E, Boscoboinik DO, Bartoli GM, et al (1993) Inhibition of smooth muscle cell proliferation and protein kinase C activity by tocopherols and tocotrienols. Biochim Biophys Acta 1176:83–89
9. Clark LC, Combs GF Jr, Turnbull BW, et al (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 276:1957–1963
10. Clark LC, Dalkin B, Krongrad A, et al (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol 81:730–734
11. Comstock GW, Helzlsouer KJ, Bush TL (1991) Prediagnostic serum levels of carotenoids and vitamin E as related to subsequent cancer in Washington County, Maryland. Am J Clin Nutr 53:260S–264S
12. Combs GF Jr, Clark LC (1997) Selenium and cancer. In: Garewal H (ed) Antioxidants and disease prevention. CRC, New York
13. Comstock GW, Bush TL, Helzlsouer K (1992) Serum retinol, beta-carotene, vitamin E, and selenium as related to subsequent cancer of specific sites. Am J Epidemiol 135:115–121
14. Doll R, Peto R (1981) The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States. J Natl Cancer Inst 66:1192–1308
15. Eichholzer M, Stahelin HB, Gey FK, et al (1996) Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. Int J Cancer 55:145–150
16. El-Bayoumy K (1991) The role of selenium in cancer prevention. In: DeVita VT, Hellman S, Rosenberg SS (eds) Practice of oncology. Lippincott, Philadelphia, pp 1–15
17. Evans HM, Bishop KS (1922) On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science 56:650–651
18. Ferraroni M, La Vecchia C, D'Avanzo B, et al (1994) Selected micronutrient intake and the risk of colorectal cancer. Br J Cancer 70:1150–1155
19. Freudenheim JL, Graham S, Horvath PJ, et al (1990) Risks associated with source of fiber components in cancer of the colon and rectum. Cancer Res 50:3295–3300
20. Hartman TJ, Albanes D, Pietinen P, et al (1998) The association between baseline vitamin E, selenium, and prostate cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Cancer Epidemiol Biomarkers Prev 7:335–340

21. Heinonen OP, Albanes D, Huttunen JK, et al (1998) Prostate cancer and supplementation with α-tocopherol and β-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst 90:440–446
22. Hsing AW, Comstock GW, Abbey H, Polk BF (1990) Serologic precursors of cancer; retinol, carotenoids, and tocopherol and risk of prostate cancer. J Natl Cancer Inst 82:941–946
23. Ip C, Medina D (1987) Current concept of selenium and mammary tumorigenesis. In: Medina D, Kidwell W, Heppner G, Anderson EP (eds) Cellular and molecular biology of breast cancer. Plenum, New York
24. Ip C, Thompson HJ, Zhu Z, Ganther HE (2000) In vitro and in vivo studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. Cancer Res 60:2882–2886
25. Israel K, Sanders BG, Kline K (1995) RRR-alpha-tocopheryl succinate inhibits the proliferation of human prostatic tumor cells with defective cell cycle/differentiation pathways. Nutr Cancer 24:161–169
26. Kiremidjian-Schumacher L, Stotzky G (1987) Review: selenium and immune response. Environ Res 42:277–303
27. Kishimoto M, Yano Y, Yajima S, Otani S, Ichikawa T, Yano T (1998) The inhibitory effect of vitamin E on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in mice based on the regulation of polyamine metabolism. Cancer Lett 126:173–178
28. Knekt P, Aromaa A, Maatala J, et al (1988) Serum vitamin E and risk of cancer among Finnish men during a 10-year follow-up. Am J Epidemiol 127:28–41
29. Knekt P, Jarvinen R, Sepannen R, et al (1991) Dietary antioxidants and the risk of lung cancer. Am J Epidemiol 134:471–479
30. Lee HP, Gourley L, Duffy SW, et al (1989) Colorectal cancer and diet in an Asian population study among Singapore Chinese. Int J Cancer 43:1007–1016
31. Li JY, Taylor PR, Li B, Dawsey S, Wang GQ, Ershow AG, Guo W, Liu SF, Yang CS, Shen Q, Wang W, Mark SD, Zou XN, Greenwald P, Wu YP, Blot WJ (1993) Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. J Natl Cancer Inst 85:1492–1498
32. Longnecker MP, Martin-Moreno JM, Knekt P, et al (1992) Serum alpha-tocopherol concentration in relation to subsequent colorectal cancer: pooled data from five cohorts. J Natl Cancer Inst 84:430–435
33. Machlin LJ (1991) Vitamin E In: LJ Machlin (ed) Handbook of vitamins, 2nd edn. Dekker, New York
34. Mahoney CW, Azzi A (1988) Vitamin E inhibits protein kinase C activity. Biochem Biophys Res Commun 154:694–697
35. Meyer F, White E (1993) Alcohol and nutrients in relation to colon cancer in middle-aged adults. Am J Epidemiol 136:225–236
36. Nakamura A, Shirai T, Takahashi S, Ogawa K, Hirose M, Ito N (1991) Lack of modification by naturally occurring antioxidants of 3,2'-dimethyl-4-aminobiphenyl-initiated rate prostate carcinogenesis. Cancer Lett 58:241–246
37. National Academy of Sciences (1989) Recommended dietary allowances, 10th edn. National Academy Press, Washington, pp 217–224
38. National Research Council (1989) Recommended dietary allowances, 10th edn. National Academy Press, Washington
39. Ocke MC, Bueno-de-Mesquita HB, Feskens EJ, et al (1997) Repeated measurements of vegetables, fruits, b-carotene, and vitamins C and E in relation to lung cancer: the Zutphen study. Am J Epidemiol 145:358–365
40. Ottino P, Duncan JR (1997) Effect of alpha-tocopherol succinate on free radical and lipid peroxidation levels in BL6 melanoma cells. Free Radic Biol Med 22:1145–1151
41. Pappas AM (1998) Vitamin E: tocopherols and tocotrienols. In: AM Pappas (ed) Antioxidant status, diet, nutrition, and health, CRC, Boca Raton
42. Redman C, Scott JA, Baines AT, Basye JL, Clark LC, Calley C, Roe D, Payne CM, Nelson MA (1998) Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. Cancer Lett 125:103–110
43. Ries LAG, Kosary CL, Hankey BF, Miller BA, Edwards BK (eds) (1998) SEER Cancer Statistics Review, 1973–1995, National Cancer Institute, Bethesda
44. Shibata A, Paganini-Hill A, Ross RK, Henderson BE (1992) Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 66:673–679
45. Shimada T, El-Bayoumy K, Upadhyaya P, Sutter TR, Guengerich FP, Yamazaki H (1997) Inhibition of human cytochrome P450-catalyzed oxidations of xenobiotics and procarcinogens by synthetic organoselenium compounds. Cancer Res 57:4757–4764
46. Sigounas G, Anagnostou A, Steiner M (1997) dl-Alpha-tocopherol induces apoptosis in erythroleukemia, prostate, and breast cancer cells. Nutr Cancer 28:30–35
47. Thompson HJ, Wilson A, Lu J, et al (1994) Comparison of the effects of an organic and an inorganic form of selenium on a mammary carcinoma cell line. Carcinogenesis 15:183–186
48. Traber MG, Packer L (1995) Vitamin E: beyond antioxidant function. Am J Clin Nutr 62:1501
49. Umeda F, Kato K-I, Muta K, Ibayashi H (1982) Effect of vitamin E on function of pituitary-gonadal axis in male rats and human studies. Endocrinol Jpn 29:287–292
50. United States Department of Agriculture (1987) Nationwide food consumption survey continuing survey of food intake by individuals: women 19–50 years and their children 1–5 years, 4 days, 1985. Report no 85-4, Nutrition and Monitoring Division, Human Nutrition Information Economic Research Service, Hyattsville
51. United States Department of Agriculture (1987) Nationwide food consumption survey continuing survey of food intake by individuals: men 19–50 years 1 day, 1985. Report no 85-3, Nutrition and Monitoring Division, Human Nutrition Information Economic research Service, Hyattsville
52. Wang W, Higuchi CM (1995) Induction of NAD(P)H:quinone reductase by vitamins A, E and C in Colo205 colon cancer cells. Cancer Lett 98:63–69
53. Webber MM, Perez-Ripoli EA, James GT (1985) Inhibitory effects of selenium on the growth of DU-145 human prostate carcinoma cells in vitro. Biochem Biophys Res Commun 130:603–609
54. Wu AH, Paganini-Hill A, Ross RK, Henderson BE (1987) Alcohol, physical activity and other factors for colorectal cancer: a prospective study. Br J Cancer 55:687–694
55. Yong LC, Brown CC, Schatzkin A, et al (1997) Intake of vitamins E, C, and A and risk of lung cancer: the NHANES I Epidemiologic Followup Study. Am J Epidemiol 146:231–243
56. Yoshizawa K, Willett WC, Morris SJ, et al (1998) Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. J Natl Cancer Inst 90:1219–1224
57. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 342:145–153